## REMARKS

### I. Amendments

Claims 1-5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 were examined. Claims 1-3, 5, 8, 10-12, 23, 32, 33, 35 and 42 have been amended. The amendments to the claims do not add or constitute new matter. Support for the amendments may be found throughout the specification and originally filed claims.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 1-5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 are pending in the instant application.

### II. Objections

The Examiner has objected to claim 1 because it contains two steps (b), and requested appropriate correction. Applicants have amended claim 1 to change the second step (b) to correctly recite step (c). As a result, the objection is no longer relevant.

### III. Rejections

#### *A. Rejection under 35 U.S.C. § 112, first paragraph*

##### *1. Claims 10 and 23*

Claims 10 and 23 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons set forth in Paper No. 15. More particularly, the Examiner stated in Paper No. 15 (the Office Action dated December 2, 2002) that the disclosure is allegedly only enabling for the methods which utilize a mouse ES cell, whereas the claimed methods recite only an ES cell and are not limited to a mouse ES cell. Applicants respectfully traverse the rejection. However, in order to expedite prosecution, Applicants have amended claims 10 and 23 to recite a mouse ES cell, rendering this rejection moot. Applicants respectfully request withdrawal of this rejection.

*2. Claims 11, 12, 32 and 35 (New Grounds necessitated by Amendment)*

The Examiner has rejected claims 11, 12, 32, and 35 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

Specifically, the Examiner asserts that while the specification is enabling for a method of identifying an agent that ameliorates an abnormality associated with a homozygous disruption in a cGMP phosphodiesterase gene wherein said abnormality is an eye abnormality or hyperactive behavior relative to a wild-type mouse, it does not reasonably provide enablement for a method of identifying an agent that ameliorates any and all abnormalities associated with disruption of a cGMP phosphodiesterase alpha subunit gene.

The rejection specifically relates to the unpredictability of a phenotype arising from insertion or deletion of a gene, even a well-characterized gene. The Examiner asserts that the specification is only enabling for phenotypes of the mouse which have been disclosed and described in the specification. More particularly, the Examiner states that "only methods wherein the abnormality measured in the determining step is an eye abnormality or hyperactivity relative to a wild-type mouse are enabled by the specification." Applicants disagree with the Examiners conclusions, and believe that the specification is enabling for the methods as claimed in that they utilize a mouse exhibiting a specific phenotype enabled by the specification. However, Applicants have amended these claims in order to expedite prosecution of the instant application. As amended, the claims are now limited to determining whether the agent modulates a specific abnormality (an eye abnormality, hyperacitivity or both), as suggested by the Examiner.

As a result of the amendment, this rejection under 35 U.S.C. § 112, first paragraph, is no longer relevant, and withdrawal of the rejection is respectfully requested. Applicants submit that the pending claims now fully meet the enablement requirements and are patentable under 35 U.S.C. § 112, first paragraph.

*3. Claims 5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 (New Grounds)*

The Examiner has rejected claims 5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because they allegedly contain subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner states that although it was previously indicated that cells and mice limited to comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit gene and having a phenotype selected from an eye abnormality or hyperactivity are adequately described by the teachings of the specification, adequate written description of a transgenic mouse requires description of both the genotype and phenotype of the mouse. More particularly, the Examiner states that "only transgenic mice comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit, wherein production of the cGMP phosphodiesterase alpha subunit is completely inhibited" meet the written description requirement.

Applicants respectfully disagree with the Examiner. Applicants submit that the specification clearly describes the phenotype and genotype of the transgenic mice recited in these claims. However, Applicants have amended these claims to recite transgenic mice comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit gene, which mice "lack production of functional cGMP phosphodiesterase alpha subunit protein" and exhibit phenotypes including an eye abnormality or hyperactive behavior. Applicants believe that this language adequately describes the genotype or disruption as required by the Examiner. As a result of this amendment, the written description rejection of these claims is no longer relevant, and Applicants respectfully request its withdrawal.

Applicants submit that pending claims 1-5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 fully meet the written description requirements and are patentable under 35 U.S.C. § 112, first paragraph.

***B. Rejections under 35 U.S.C. § 112, second paragraph***

*1. Claim 32 (New Grounds Necessitated by Amendment)*

The Examiner has rejected claim 32 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner asserts that recitation of "the phenotype" in step (b) renders the claim indefinite because it is unclear whether the phenotype is limited to the eye abnormality or is directed to any phenotype including those also comprised by the mouse but not identified.

The Examiner states that the "rejection can be overcome by clearly stating the phenotype to be determined in part (b) of the claim."

Applicants respectfully traverse the rejection. However, Applicants have adopted the Examiner's suggestion, and amended the claim to recite the eye abnormality. Therefore, this rejection under 35 U.S.C. § 112, second paragraph, is no longer relevant, and Applicants respectfully request withdrawal of the rejection.

*2. Claims 1-3 (New Grounds)*

Claims 1-3 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the Examiner asserts that these claims are indefinite in the recitation of "selectable marker" and "screening marker" because it is unclear whether Applicants intend that the claims be limited to a marker that can be detected directly or whether the vectors actually comprise genes encoding selectable or screening markers as is more commonly used in the art. The Examiner suggests amending the claims to indicate that the constructs comprise a "selectable marker gene" or a "screening marker gene". Applicants have amended the claims to recite "selectable marker gene" or "screening marker gene" as suggested. As a result, this rejection is no longer relevant, and Applicants respectfully request its withdrawal.

Applicants submit that the pending claims are definite and clearly point out and distinctly claim the subject matter which Applicants regard as the invention as required by 35 U.S.C. § 112, second paragraph.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-849.

Respectfully submitted,

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